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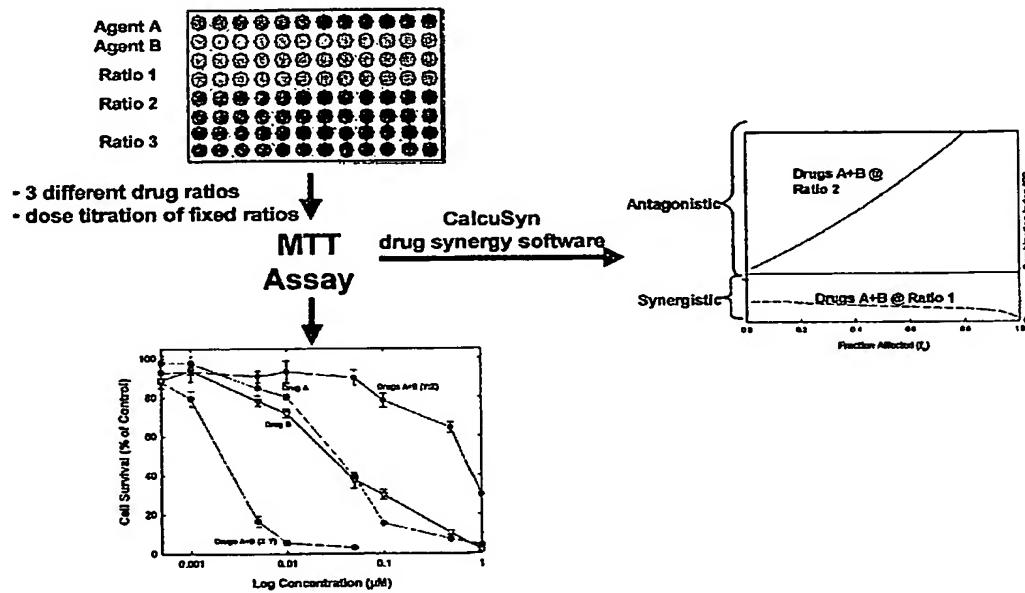
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[Continued on next page]

(54) Title: METHODS TO INDIVIDUALIZE COMBINATION THERAPY



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(57) Abstract: Compositions which comprise delivery vehicles having stably associated therewith predetermined, patient-specific combinations of two or more agents, such as antineoplastic agents, are useful in achieving optimal therapeutic effects on a patient-by-patient basis when combinations of drugs are administered.



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:  
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# INTERNATIONAL SEARCH REPORT

International Application No  
/US2004/010388

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 G01N33/50 A61K39/00 A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BEPLER G ET AL: "ADDITIVE AND DIFFERENTIAL BIOLOGICAL ACTIVITY OF ALPHA INTERFERON A DIFLUOROMETHYLORNITHINE AND THEIR COMBINATION ON ESTABLISHED HUMAN LUNG CANCER CELL LINES"  <i>CANCER RESEARCH</i>,          vol. 46, no. 7, 1986, pages 3413-3419,          XP009036764          ISSN: 0008-5472          abstract          page 3417, left-hand column, last paragraph - right-hand column, last paragraph</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-16, 22-25



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

23 September 2004

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07/10/2004

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## INTERNATIONAL SEARCH REPORT

International Application No  
/US2004/010388

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>OSAKI S-I ET AL: "Alteration of drug chemosensitivity caused by the adenovirus-mediated transfer of the wild-type p53 gene in human lung cancer cells"            CANCER GENE THERAPY 2000 UNITED STATES,            vol. 7, no. 2, 2000, pages 300-307,            XP002297132            ISSN: 0929-1903            abstract</p> <p>-----</p>	1-16, 22-25
A	<p>VAN'T VEER LAURA J ET AL: "Gene expression profiling predicts clinical outcome of breast cancer"            NATURE (LONDON),            vol. 415, no. 6871,            31 January 2002 (2002-01-31), pages            530-536, XP002297133            ISSN: 0028-0836            cited in the application            abstract            page 534, right-hand column, last            paragraph - page 535, left-hand column,            paragraph 1</p> <p>-----</p>	1-16, 22-25
P, X	<p>BLUMENTHAL ROSALYN D ET AL: "An in vitro model to optimize dose scheduling of multimodal radioimmunotherapy and chemotherapy: Effects of p53 expression."            INTERNATIONAL JOURNAL OF CANCER,            vol. 108, no. 2,            10 January 2004 (2004-01-10), pages            293-300, XP009036653            ISSN: 0020-7136            abstract</p> <p>-----</p>	1-16, 22-25

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. The same remark applies to claims 22 to 25 which encompass method steps carried out on the human/animal body.

Continuation of Box II.2

Claims Nos.: 17-21

The compositions in claims 17 and 18 are defined by reference to a method of preparation which definition does not characterise the "therapeutic agents" neither the "ratio of the first to the second therapeutic agent". The single characterising features which are imparted to the composition by its method of preparation are the presence of two therapeutic agents, each associated with a delivery vehicle. However, the number of compositions which fall within this definition is so large that a meaningful search for said claims is rendered impossible. It is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

The same objection applies to the claims defining uses of said compositions, for the same reasons. Therefore, the subject-matter of claims 19 to 21 cannot be searched in a meaningful way.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/010388

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. The same remark applies to claims 22 to 25 which encompass method steps carried out on the human/animal body.
2.  Claims Nos.: 17-21  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  

see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.